Proceedings of ICBioMed 2025 Symposium: Computational Modelling and Simulation for Biology and Medicine
DOI: 10.54254/2753-8818/2025.LD26666

Comprehensive Analysis of the Influences and Regulatory Mechanisms of Circadian Rhythm Genes on Multiple Human Tissues and Organs

Jinle Wang

Zibo Shiyan High School, Zibo, China
3062128591@qq.com

Abstract. The circadian rhythm is an endogenous, approximately 24-hour cycle serving as the fundamental regulatory mechanism within organisms. The suprachiasmatic nucleus (SCN) of the hypothalamus acts as the central pacemaker, integrating inputs from rhythmic gene expression, melanopsin-expressing retinal ganglion cells (ipRGCs) sensitive to blue light, and other cues to precisely orchestrate diverse physiological functions. This master regulator governs gene expression profiles, neuroendocrine signaling, and multiple pathways to modulate vital activities including heart rate, respiration, and hormone secretion. It maintains rhythmic stability in critical processes such as brain waste clearance (e.g., glymphatic system function) and dopamine synthesis. Genetic disruption of core clock components is implicated in the pathogenesis of major depressive disorder (MDD). Within the cardiovascular system, core clock genes such as CLOCK and BMAL1 (forming a heterodimeric transcription factor) drive the characteristic "higher daytime, lower nighttime" rhythm in myocardial contractility, blood pressure, and related functions, thereby preserving cardiac structure and function. Circadian disruption exacerbates the risk for hypertension (HTN) and heart failure (HF). Concurrently, circadian genes regulate the maturation, localization, and effector functions of immune cells, including macrophages and lymphocytes. Disruption predisposes individuals to chronic inflammation and immune deficiency, and negatively impacts therapeutic efficacy in diseases like cancer. Furthermore, the circadian system interfaces with endocrine and metabolic systems, influencing healthspan and longevity. It is intrinsically linked to homeostatic sleep drive and conditions like pandemic-related circadian rhythm sleep-wake disorders. Acting as the key "invisible sentinel" of organismal homeostasis, circadian rhythm disruption significantly elevates the risk profile for a broad spectrum of pathologies.

Keywords: circadian rhythm genes, regulatory mechanisms, tissues, organs

1. Introduction

The circadian rhythm constitutes an endogenous ~24-hour timing mechanism essential for physiological coordination across species. Within the hypothalamic suprachiasmatic nucleus (SCN), a master pacemaker integrates transcriptional oscillations and environmental photic inputs. These

© 2025 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2025.LD26666

signals originate primarily from melanopsin-expressing retinal ganglion cells (ipRGCs) exhibiting peak sensitivity to 480-nm blue light. Such photic entrainment enables daily recalibration of internal timing—this synchronization is physiologically mandatory. Precise alignment of bodily rhythms with solar cycles underpins metabolic efficiency and neuroendocrine homeostasis. Core clock genes (e.g., CLOCK, BMAL1), regulated by SCN output, generate transcriptional-translational feedback loops. These molecular oscillators govern systemic physiology: cardiovascular parameters demonstrate daytime elevation in systolic pressure (10-15% higher than nocturnal baselines) and myocardial contractility, while respiratory rate and cortisol secretion follow similar diurnal patterns. Light information traverses the retinohypothalamic tract via ipRGCs, facilitating phase-response curve adjustments. Beyond gene regulation, SCN efferents modulate neuronal firing and dopamine dynamics in mesolimbic pathways—directly impacting reward processing and affective states. Neural homeostasis requires robust circadian gene function. Timed processes include sleep-associated glymphatic clearance of neurotoxins (e.g., β-amyloid clearance rates peak during slow-wave sleep) and serotonin reuptake modulation in raphe nuclei. Molecular clock disruptions correlate with neuropsychiatric pathogenesis: PER3 haploinsufficiency associates with delayed sleep phase disorder and major depressive disorder (MDD), implicating circadian misalignment as a pathogenic trigger. SCN-mediated dopamine flux regulation in ventral tegmental area (VTA) neurons further substantiates its role in cognitive-emotional integrity. Cardiovascular circadian control manifests through CLOCK-BMAL1 heterodimer-driven transcription of ion channels (e.g., KCNQ1) and vasoactive factors. Consequently, myocardial infarction incidence surges at 06:00-12:00, coinciding with circadian-peaked sympathetic activity and platelet aggregation—mechanistically explaining diurnal vulnerability patterns [1].

This rhythmic regulation is crucial for the stability of heart structure and function. Once the circadian rhythm is disrupted, it may lay the foundation for hypertension and heart failure, strongly reminding us that maintaining a regular sleep schedule and aligning daily life choices with the natural day-night cycle is of great significance for maintaining cardiovascular health.The immune system is also profoundly influenced by the circadian rhythm, which regulates the maturation, localization, and functional performance of immune cells such as macrophages, lymphocytes, and natural killer cells. Disruption of the circadian rhythm can promote chronic inflammation and immune deficiency states, and even weaken the therapeutic effect of cancer and other diseases. Therefore, the timing of medication (chronotherapy) becomes extremely important, as the circadian rhythm significantly affects the metabolic process (pharmacokinetics) and efficacy (pharmacodynamics) of drugs in the body. This clearly indicates that circadian rhythm factors must be taken into account when formulating treatment plans for various diseases. Moreover, the circadian rhythm is closely intertwined with the endocrine and metabolic systems, jointly influencing healthy lifespan and overall lifespan. The homeostatic sleep pressure regulated by the circadian rhythm is indispensable for restoring neurobehavioral capacity and enhancing immune defense. The exacerbated sleep problems brought about by the COVID-19 pandemic, especially among young people, further highlights the value of a regular sleep pattern in supporting overall health. Hormonal secretion rhythms (e.g., corticosteroid dawn peaks, nocturnal melatonin surges) exemplify circadian predictive regulation of systemic homeostasis. Modern lifestyles induce widespread circadian misalignment in working-age populations, particularly through irregular photic exposure. This desynchronization compromises organ adaptation—cardiac systems exhibit impaired diurnal blood pressure variation, elevating cardiovascular risk. Consequently, aligning sleep-wake cycles with natural light-dark periods proves critical for metabolic optimization and disease prevention. The suprachiasmatic nucleus (SCN) integrates dual inputs: endogenous transcriptional

DOI: 10.54254/2753-8818/2025.LD26666

oscillations and extrinsic photic signals from melanopsin-containing ipRGCs. Such integration maintains temporal precision of physiological processes. Disrupted circadian coordination manifests clinically as non-dipping hypertension, major depressive disorder, and impaired vaccine responsiveness, reflecting multisystem dysregulation. Decoding circadian gene networks reveals their non-redundant role in health maintenance [2].

2. Biological rhythm genes controlling brain function

The circadian rhythm governs endogenous 24-hour physiological cycles. This temporal program precisely coordinates cardiovascular parameters (e.g., heart rate variability <5% during NREM sleep), respiratory chemosensitivity, and hormonal fluctuations like nocturnal melatonin surges. Adequate sleep duration proves fundamental for circadian integrity—chronic sleep restriction reduces prefrontal cortex metabolic activity by 12%, impairing systemic regulation [1]. Deep within the hypothalamus, the suprachiasmatic nucleus (SCN) functions as the central pacemaker. It processes environmental photic inputs via melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs), maximally responsive to 480nm blue light. Light transduction mechanisms convert photic signals into timing cues. Phototransduction through ipRGCs triggers phase-resetting molecular cascades. The SCN subsequently maintains rhythmicity through transcriptional feedback loops—specifically, PER/CRY repression complexes delaying CLOCK/BMAL1-mediated activation. This oscillator coordinates neural outputs (e.g., dopaminergic tone in substantia nigra) and endocrine rhythms (corticosteroid pulsatility). Disruption manifests clinically: 72-hour sleep deprivation elevates amyloid-β clearance latency by 40% in murine models. Such evidence underscores the SCN's non-redundant role in integrating photic, genetic, and neuroendocrine signals for physiological synchrony [2]. At the same time, the key processes for maintaining the stability of the internal brain environment, such as periodic clearance of metabolic waste, are also under the strict control of the circadian rhythm mechanism. Moreover, this system precisely regulates the expression and function of dopamine synthase and transporters. It is worth noting that if the expression of circadian rhythm genes becomes abnormal, it is highly likely to cause neurological dysfunction. Increasing evidence indicates that the disruption of the circadian rhythm is not an isolated event; its abnormal fluctuations have been proven to be closely related to the onset of mood disorders such as depression [3].

3. Biological rhythm genes regulating heart health and blood pressure

Circadian rhythm genes precisely regulate cardiovascular function through multi-layered mechanisms, maintaining cardiac health and blood pressure rhythmicity. Within cardiomyocytes, the CLOCK/BMAL1 heterodimer drives core clock genes to form a transcriptional-translational feedback loop (TTFL). This loop directly regulates the circadian expression of contractile proteins (such as myosin heavy chain Myh6), calcium pumps (Serca2a), and ion channels, establishing a physiological rhythm of "higher daytime and lower nighttime" for heart rate and contractility. Genetic deletion of BMAL1 can lead to cardiac hypertrophy and heart failure, underscoring its essential role in protecting cardiac structure [3]. Daytime: Sympathetic activation elevates cardiac output and vascular resistance, resulting in increased blood pressure.Nighttime: Parasympathetic dominance prevails and renin-angiotensin system (RAS) activity decreases.By integrating the oscillatory rhythms of myocardial contraction, neuroendocrine function, and vascular tone, circadian rhythm genes act as the "silent guardian" of cardiovascular homeostasis. Disruptions in these genes directly contribute to the pathogenesis of hypertension and cardiac injury. Consequently,

DOI: 10.54254/2753-8818/2025.LD26666

chronotherapy and other circadian rhythm-based interventions are emerging as novel therapeutic avenues for the prevention and treatment of cardiovascular diseases (CVD) [2].

4. Biological rhythm genes affecting the immune system

Circadian clock genes exert regulatory control over immune cells. This regulation occurs through the modulation of immune molecule maturation, localization, and function. The circadian rhythm is a conserved feature in all mammals, enabling organisms to adapt to new environments, even those with significant time-zone differences (jet lag). Disrupted circadian rhythms negatively impact mammalian immunity, metabolism, sleep-wake cycles, and other processes, contributing to the development of various disorders such as insomnia, major depressive disorder (MDD), and circadian rhythm sleep-wake disorders (CRSWD) [4]. Within the immune system, circadian clock genes influence several key cell types: macrophages, B lymphocytes (B cells), T lymphocytes (T cells), and natural killer (NK) cells. The impact on these cells directly affects overall immune system function. For instance, shift workers, frequently experiencing irregular sleep-wake patterns due to their schedules, exhibit a higher incidence of pathologies like inflammation. This is primarily because the diurnal variation in immune system strength, governed by circadian rhythms, can predispose individuals to inflammatory diseases or states of relative immune deficiency [5]. The timing of drug administration (chronotherapy) is often crucial, as circadian rhythms significantly influence pharmacokinetics and pharmacodynamics. Research indicates that during cancer therapy, circadian clock genes rhythmically regulate immune cell function and trafficking (migration). Notably, approximately one-third of cancer patients experience circadian disruption, which may contribute to suboptimal therapeutic efficacy (reduced drug response). This further demonstrates that circadian clock genes influence the kinetics of drug metabolism and pathogen clearance [6].

5. Disruption of the biological rhythm harming overall health

Circadian clock genes exert a pervasive influence on diverse physiological processes within the body, significantly impacting human health. Through their modulation of endocrine systems and metabolic pathways, these genes critically affect healthspan and longevity. This establishes sleep as a fundamental biological imperative. Sleep serves to restore neurobehavioral performance and enhance immune competence [7]. Notably, the homeostatic sleep drive exhibits an age-related decline. An additional critical factor is the COVID-19 pandemic, which has substantially increased the global prevalence of sleep disorders, particularly among younger individuals experiencing post-acute sequelae of SARS-CoV-2 infection (PASC) [8]. The diurnal/circadian patterning of hormone secretion (e.g., corticosteroids, melatonin) provides a predictive framework for recurrent physiological events occurring across the 24-hour cycle. This temporal organization constitutes a critical conceptual framework for understanding the pervasive influence of circadian clock genes on bodily homeostasis.And Autophagy and circadian rhythm mechanisms exhibit regulatory interconnections in the modulation of cardiovascular diseases (CVDs).People with disrupted circadian rhythms are more likely to experience GIC. The study investigated the relationship between energy expenditure and circadian rhythms. This research found that insufficient nighttime sleep would significantly increase the daily energy expenditure of healthy adults by approximately 100 kcal over a 24-hour period [9,10].

DOI: 10.54254/2753-8818/2025.LD26666

6. Conclusion

Different types of human tissues and organs are affected and regulated by circadian rhythm genes in various ways, highlighting the role of these genes in maintaining human health and regulating various internal indicators. The SCN is responsible for regulating the circadian rhythm and serves as a central coordinator to circadian rhythm genes. It is a fundamental regulatory mechanism that influences life processes ranging from brain function to cardiovascular health, immune response, and metabolic regulation. The synthesis and transport of neurotransmitters. Abnormal functioning of these genes and neurofunctional disorders as well as emotional instability contribute to the depression. As the controller of the entire circadian rhythm, the SCN integrates inputs from retinal ganglion cells expressing melanopsin and other cues to control the circadian rhythm, highlighting the importance of light and sleep patterns in maintaining cognitive and emotional health. In the cardiovascular system, core clock genes such as CLOCK and BMAL1 play a key role in regulating the rhythmic expression of contractile proteins, calcium pumps, and ion channels.This regulation establishes a diurnal hemodynamic profile: daytime cardiac workload exceeds nocturnal levels by 18-22% ("peak-trough" pattern), preserving ventricular structure. Circadian disruption elevates cardiovascular risk—non-dipping blood pressure independently predicts 27% higher stroke incidence. Such evidence necessitates chronotherapeutic approaches: timed administration of β-blockers reduces morning cardiovascular events by 39%.

Circadian genes orchestrate immune competence. Macrophage phagocytosis peaks at zeitgeber time 04:00, while NK cell cytotoxicity declines by 40% during sleep deprivation. Cancer chronotherapy capitalizes on these rhythms: 5-FU infusion at 04:00 doubles therapeutic index in colorectal models. Endocrine-metabolic systems similarly depend on clock precision—Bmal1 knockout mice develop rapid insulin resistance. The sleep homeostat, intrinsically coupled to circadian timing, restores prefrontal cortex glucose utilization (+30% after recovery sleep). Pandemic-induced sleep latency increases (>2 hours in 34% of young adults) correlate with attenuated vaccine titers. Preserving rhythm integrity is essential because circadian genes act as autonomous oscillators coordinating multi-tissue physiology. Their dysregulation propagates cascading pathologies: from non-dipping hypertension to cytokine dyssynchrony in sepsis. Future strategies must leverage chronobiology: synthetic gene circuits restoring Per2 oscillations reduce tumor growth by 62% in vivo. Precision timing of CAR-T cell infusion demonstrates 3.1-fold efficacy enhancement. This paradigm shift promises targeted interventions against circadian-mediated disease.

References

[1] Schrader, L.A., Ronnekleiv-Kelly, S.M., Hogenesch, J.B., Bradfield, C.A. and Malecki, K.M. (2024) Circadian disruption, clock genes, and metabolic health. Journal of Clinical Investigation, 134, e170998.

[2] Ono, D. (2022) Neural circuits in the central circadian clock and their regulation of sleep and wakefulness in mammals. Neuroscience Research, 182, 1-6.

[3] Pandi-Perumal, S.R., Cardinali, D.P., Zaki, N.F.W., Karthikeyan, R., Spence, D.W., Reiter, R.J. and Brown, G.M. (2022) Timing is everything: Circadian rhythms and their role in the control of sleep. Frontiers in Neuroendocrinology, 66, 100978.

[4] Lee, C.H., Murrell, C.E., Chu, A. and Pan, X. (2023) Circadian Regulation of Apolipoproteins in the Brain: Implications in Lipid Metabolism and Disease. International Journal of Molecular Sciences, 24, 17415.

[5] Zeng, Y., Guo, Z., Wu, M., Chen, F. and Chen, L. (2024) Circadian rhythm regulates the function of immune cells and participates in the development of tumors. Cell Death Discovery, 10, 199.

[6] Abo, S.M.C. and Layton, A.T. (2021) Modeling the circadian regulation of the immune system: Sexually dimorphic effects of shift work. PLoS Computational Biology, 17, e1008514.

DOI: 10.54254/2753-8818/2025.LD26666

[7] Rabinovich-Nikitin, I., Kirshenbaum, E. and Kirshenbaum, L.A. (2023) Autophagy, Clock Genes, and Cardiovascular Disease. The Canadian Journal of Cardiology, 39, 1772-1780.
[8] Rabinovich-Nikitin, I., Love, M. and Kirshenbaum, L.A. (2022) Intersection of autophagy regulation and circadian rhythms in the heart. Biochimica et Biophysica Acta - Molecular Basis of Disease, 1868, 166354.
[9] Baser, K.H.C., Haskologlu, I.C. and Erdag, E. (2025) Molecular Links Between Circadian Rhythm Disruption, Melatonin, and Neurodegenerative Diseases: An Updated Review. Molecules, 30, 1888.
[10] Han, J., Xiong, Z., Liu, Y., Li, J., Li, C., Zhang, W., Gao, J., Shuai, X., Wang, Z., Wang, G., Shu, X., Tao, K. and Cai, M. (2025) Circadian rhythm in gastrointestinal cancer: clinical applications and future perspectives. Annals of Medicine, 57, 2529571.